IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

Manne Satyanarayana REDDY et al. Art Unit: 1625

Application No.: 10/647,449 Examiner: C.C. Chang

Filed: August 25, 2003

For: POLYMORPHIC FORMS OF (S)-REPAGLINIDE AND THE PROCESSES FOR PREPARATION THEREOF

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

REPLY BRIEF

This paper is submitted in response to the Examiner's Answer mailed November 30, 2006, for the above-identified application, and addresses arguments that were newly set forth in the Examiner's Answer. Submission of a reply brief in response to the Examiner's Answer is due by January 30, 2007. Accordingly, this reply brief is being timely filed.

1. Status of the Claims

Claims 1-57 were finally rejected in an Office Action mailed on March 6, 2006, although claims 3, 39, 49, 52 and 55 were previously canceled in an amendment submitted on December 1, 2005. Accordingly, claims 1-2, 4-38, 40-48, 50, 51, 53, 54, 56 and 57 are considered to be the subject of this appeal.

2. Grounds of Rejection for Review on Appeal

A. Whether claims 38 and 40-48 are anticipated under 35 U.S.C. § 102(b) by Grell et al (U.S. Patent No. 5,312,924; "Grell I").

B. Whether claims 1, 34 and 35 are anticipated under 35 U.S.C. § 102(b) by Grell I.

C. Whether claims 1, 2, 4-37, 50, 51, 53, 54, 56 and 57 are unpatentable under 35 U.S.C. § 103(a) over Grell I in view of Grell et al. (*J. Med. Chem.*, 1998, 41:5219-5246; "Grell II") and Brittain, ed. (Polymorphism in Pharmaceutical Sciences, 1999, pp. 179-79, 185, 219; "Brittain").

D. Whether claims 8-18 are invalid under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement requirement.

3. Argument

A. Rejection of Claims 38 and 40-48 Under 35 U.S.C. § 102(b)

Claims 38 and 40-48 stand finally rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Grell I. According to the Examiner in the Examiner's Answer mailed November 30, 2006 ("Examiner's Answer"), columns 89-90 of Grell I disclose non-crystalline (S)-repaglinide "after vacuo of solvent ethanol." This solid, according to the Examiner, is amorphous and the process is the same as that claimed. The original explanation of this rejection, in the Office Action that was mailed on July 15, 2005 ("7/15/05 Office Action"), erroneously referred to column 23, lines 15-17 of Grell I.

Appellants indicated in their Appeal Brief filed September 6, 2006 ("Appellants' Appeal Brief"), that column 23, lines 15-17 of Grell I is not even directed to repaglinide (2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl]-aminocarbonylmethyl]-benzoic acid), but rather to the compound 2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-1-butyl]-aminocarbonylmethyl]-benzoic acid.

In the interest of completeness, however, Appellants noted that other portions of Grell I appear to disclose the preparation of (S)-repaglinide. Appellants noted that none of these disclosures teach amorphous (S)-repaglinide having an X-ray powder diffraction pattern substantially as shown in Figure 4 of the instant specification. For example, Example 3 at column 85, lines 40-56 discloses the preparation of (S)-repaglinide from ethyl (S)-2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl]-aminocarbonylmethyl]-benzoate, whereby the high melt crystalline form of (S)-repaglinide is obtained. Similarly, Example 11 at column 89, lines 46-59 discloses the

preparation of (S)-repaglinide from t-butyl (S)-2-ethoxy-4-[N-{1-(2-piperidino-phenyl)-3-methyl-1-butyl]-aminocarbonylmethyl]-benzoate, but again the high melt crystalline form of (S)-repaglinide is obtained.

Appellants then noted that Example 106 at column 58, line 35 to column 59, line 5, Example 10 at column 89, lines 26-45 and Example 12, column 89, line 60 to column 90, line 14, of Grell I each disclose the preparation of crystalline (S)-repaglinide involving evaporation steps, but Appellants noted that the Examiner had not provided any evidence or scientific reasoning to establish that the evaporation product is amorphous (S)-repaglinide, let alone amorphous (S)-repaglinide having an X-ray powder diffraction pattern substantially as shown in Figure 4 of the instant specification.

Appellants further noted that claims 40-48 are directed to a process for making an amorphous form of (S)-repaglinide having an X-ray powder diffraction pattern substantially as shown in Figure 4, the process comprising: (a) providing a solution of (S)-repaglinide in a lower alcohol; (b) cooling said solution so that a solid mass separates; and (c) isolating said separated solid mass to provide the amorphous form of (S)-repaglinide. In contrast, none of the above-described passages from Grell I involve cooling a (S)-repaglinide/lower alcohol solution such that a solid mass separates.

In the Examiner's Answer, the Examiner stated that when (S)-repaglinide is evaporated from ethanol, as in Grell I, the resulting compound is amorphous. Two new references were provided as supporting the Examiner's position. The Examiner first quoted from Bernstein, "Polymorphism in Molecular Crystals," p. 254 (2002) ("Bernstein") for the proposition that "amorphous pharmaceutical [materials are typically obtained by] . . . rapid solidification from the melt, lyophilization or spray drying, removal of solvents . . ." The Examiner then cited Ronsen et al. (U.S. Patent No. 5,672,612; "Ronsen") as teaching that rotary evaporation as well as spray drying will produce an amorphous form which has essentially the same X-ray diffraction pattern as Figure 4 of the instant specification.

Contrary to the Examiner's position in the Examiner's Answer, Bernstein and Ronsen do not support the conclusion that when (S)-repaglinide is evaporated from ethanol, as in Grell I, the resulting compound is necessarily amorphous. As discussed in Appellants' Appeal Brief, Grell I is silent as to the form of (S)-repaglinide made by

evaporation. MPEP § 2112 makes clear that in applying an inherency rejection of this nature, the evidence must show that the so-called "unknown property" is necessarily present in the described material:

> The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted) (The claims were drawn to a disposable diaper having three fastening elements. The reference disclosed two fastening elements that could perform the same function as the three fastening elements in the claims. The court construed the claims to require three separate elements and held that the reference did not disclose a separate third fastening element, either expressly or inherently.).

Here, the extrinsic evidence relied upon by the Examiner, Bernstein and Ronsen, does not make absolutely clear that the evaporated (S)-repaglinide from Grell I is necessarily amorphous. Although Bernstein does state that amorphous pharmaceutical material may be obtained by "removal of solvent," Bernstein goes on to state in the same sentence that such removal of solvent is from a solvate, which point the Examiner failed to include in the Examiner's Answer. Nowhere does Grell I disclose, or even suggest, that the (S)-repaglinide is a solvate or hydrate. The Examiner's reliance on Bernstein merely adds another layer of possibility to that of Grell I.

Ronsen, on the other hand, describes the amorphous preparation of a completely different drug, paroxetine hydrochloride, by vacuum or spray drying. Critically, the paroxetine hydrochloride is provided as a paroxetine hydrochloride/ethanol composition, *see* col. 2, lines 11-16, consistent with Bernstein's teaching that amorphous drugs can

prepared by desolvation of a solvate. As with Bernstein, this adds nothing but more possibility to the teachings of Grell I.

In addition, even assuming Grell I disclosed evaporation (i.e., desolvation) of a (S)-repaglinide solvate or hydrate (which it does not), Doelker, *Ann. Pharm. Fr.*, 60:161-176 (2002) ("Deolker"), cited by the Examiner as supporting Rejection (D) discussed *supra*, describes on pp. 29-33 of the English translation the preparation of various solid state forms, including crystalline forms, by desolvation. Thus, according to Doelker, although amorphous pharmaceutical material may be obtained by desolvation, it is not true that amorphous products necessarily result from desolvation. This is insufficient to support a rejection based upon anticipation by inherency.

Accordingly, Appellants maintain that claims 38 and 40-48 are not anticipated by Grell I under § 102(b), and the rejection should not be sustained.

B. Rejection of Claims 1, 34 and 35 Under 35 U.S.C. § 102(b)

Claims 1, 34 and 35 stand finally rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Grell I. According to the Examiner in the Office Action mailed March 6, 2006, the instant product and the product of Grell I are essentially the same, based on infrared absorption ("IR") spectra (comparing Figure 4 of the instant specification with Figures 2 and 3 of Grell I). The Examiner stated that no evidence exists in the record showing that the instant crystalline form and forms A, B and C of Grell I are different, especially in view of the margin of error for X-ray diffraction patterns.

In their Appeal Brief, Appellants took exception with the Examiner's characterization of the IR spectra at issue. The IR spectrum from the instant specification (shown in Figure 3, not Figure 4 as the Examiner maintained) was obtained on solid crystalline Form III of (S)-repaglinide. *See* page 17, ¶ 0055. In contrast, the IR spectra shown in Figures 2 and 3 of Grell I were obtained on racemic repaglinide in methylene chloride solution. *See* col. 32, lines 15-68. Thus, contrary to the Examiner's contention, the IR spectra do not demonstrate that instant product and the product of Grell I are essentially the same.

Appellants then noted that evidence does exist in the record, in the form of X-ray diffraction patterns disclosed in the instant specification, clearly demonstrating that that

the instant and prior art products are different. Table 6 shows the X-ray diffraction peaks for crystalline Form III of (S)-repaglinide, while Tables 1 and 2 show the X-ray diffraction peaks for (S)-repaglinide re-precipitated from racemic repaglinide using the solvent systems described in Grell I. Even a cursory inspection of the data in these Tables reveals that the X-ray diffraction pattern for crystalline Form III of (S)-repaglinide is distinctly different from that for (S)-repaglinide obtained from the solvent systems described in Grell I. In addition, the instant specification lists the melting point of crystalline Form III of (S)-repaglinide as 80-84° C (*see* pages 25-27, ¶¶ 0079-0083), while Grell I lists the melting points for two crystalline forms of (S)-repaglinide as 130-131° (high-melting form) or 99-101° C (low-melting form) (*see* col. 85, line 40 to col. 86, line 11). Appellants submitted that such evidence indicates that crystalline Form III of (S)-repaglinide recited in claims 1, 34 and 35 is patentably distinct from the prior art products disclosed in Grell I.

In the Examiner's Answer, the Examiner maintained that the IR spectra of the instant product and the product of Grell I (identified as form A) are identical, now providing a side-by-side comparison of Figure 3 of the instant specification with parts I and II of Figure 4 of Grell I. According the Examiner, the newly cited state of the art reference Baumann et al., *Helvetica Chimica Acta* 41: 2362-2379 (1958) ("Baumann"), shows that it is conventional skill well known in the art that IR differentiates stereoisomers and racemates. Therefore, it was asserted that when two products display identical IR but are merely different by private naming, they are the same product, i.e., anticipated.

Regarding the difference in X-ray diffraction patterns, the Examiner quoted from the U.S. Pharmacopeia #23 of record and the newly cited Davidovich et al., *Am. Phar. Rev.* 7:10, 12, 14, 100 (2004) ("Davidovich") for the proposition that small changes in powder X-ray patterns can arise as artifacts rather than polymorphism. The Examiner also cited Bernstein at pp. 272-273 as evidence that different compounds can display identical X-ray diffraction patterns and that the appearance of new X-ray diffraction peaks does not necessarily indicate the presence of a new polymorph. Thus, according to the Examiner, although X-ray diffraction is a useful tool, it is not an absolute

determination of true polymorphism, particularly in this case where the IR spectra show such close similarity.

Appellants maintain that all the evidence of record indicates that the instant crystalline Form III of (S)-repaglinide and the Form A of Grell I are indeed different compounds. To begin with, the IR spectrum shown in Figure 3 from the instant specification was obtained on crystalline Form III of (S)-repaglinide (*see* page 17, ¶ 0055). In contrast, the IR spectrum shown in Figure 4 of Grell I was obtained on crystalline racemic repaglinide (*see* col. 32, lines. 15-68). Thus, regardless of the similarities between the IR spectra, the fact remains that the instant Form III and Form A of Grell I are crystalline forms of different compounds.

Furthermore, the side-by-side comparison of IR spectra provided by the Examiner shows that, contrary to the Examiner's position, the spectra are not identical but rather quite distinct. For example, the IR spectrum shows several peaks at approximately 1900 cm^{-1} not present in the IR spectrum for Form A of Grell I, consistent with the Examiner's description of the teaching of Baumann. A closer examination of the spectra shows as much, if not more, difference between the instant crystalline Form III of (S)-repaglinide and Form A of racemic repaglinide of Grell I as between Forms A, B and C of Grell I (all racemic repaglinide), which are noted to be distinct solid state forms having distinct IR spectra (s*ee* Grell I, col. 32, lines 55-62 and Figs. 4-6). The distinct nature of the instant crystalline Form III of (S)-repaglinide over Form A of racemic repaglinide of Grell I is supported by the difference in their melting points: 80-84º C for the instant Form III (*see* instant specification pages 25-27, ¶¶ 0079-0083), and 90-92º C for form A of Grell I, (*see* col. 32, lines 15-40).

The X-ray diffraction data provided in Tables 1, 2 and 6 of the instant specification allow comparison of the instant crystalline Form III of (S)-repaglinide, not with Form A of racemic repaglinide of Grell I, but rather more fittingly with crystalline Forms I and II of (S)-repaglinide as prepared according to Example 3 of Grell I (*see* col. 85, line 40 to column 86, line 50). Notwithstanding the Examiner's citation to U.S. Pharmacopeia #23 and Davidovich (which is not even prior art to the instant application), Appellants maintain that the X-ray diffraction data clearly demonstrate that

the instant crystalline Form III of (S)-repaglinide and the crystalline Forms I and II of (S)-repaglinide prepared in Grell I are indeed different compounds.

Again, even a cursory inspection of the data in these Tables reveals that the X-ray diffraction pattern for crystalline Form III of (S)-repaglinide is distinctly different from that for (S)-repaglinide prepared according to Example 3 of Grell I. For example, the instant crystalline Form III of (S)-repaglinide exhibits peaks at about 4.44, 6.81, 7.80, 9.28, 11.89, 13.46, 14.34, 15.77, 16.24, 18.06, 19.25, 19.99, 21.18, 22.18, 22.58, 24.08, 25.78, 27.39, 28.03, 30.26 and 38.74 degrees two theta which are not present in the X-ray diffraction patterns obtained for Forms I and II of (S)-repaglinide of Grell I, even given the margin of error assigned for the two theta angle assignments. Such large differences are simply not the type of minor variation contemplated by Davidovich and U.S. Pharmacopeia #23 as being due to powder X-ray diffraction artifacts rather than true polymorphism. That the instant crystalline Form III of (S)-repaglinide is indeed a distinct polymorph from Forms I and II of (S)-repaglinide of Grell I is supported by their respective melting points: 80-84° C for the instant Form III (*see* pages 25-27, ¶¶ 0079-0083), and 130-131° for Form I (high-melting form) and 99-101° C for Form II (low-melting form) of Grell I (*see* col. 85, line 40 to col. 86, line 11).

Accordingly, Appellants maintain that claims 1, 34 and 35 are not anticipated by Grell I under § 102(b), and the rejection should not be sustained.

C. Rejection of Claims 1, 2, 4-37, 50, 51, 53, 54, 56 and 57 Under 35 U.S.C. § 103(a)

Claims 1, 2, 4-37, 50, 51, 53, 54, 56 and 57 stand finally rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Grell I in view of Grell II and Brittain. According to the Examiner in the 3/6/06 Office Action, even assuming that the X-ray diffraction pattern is different from the product of the art, it is, in the strictest sense, the same pure substance of the prior art, i.e., *prima facie* obvious unless some form of unobviousness can be provided. The Examiner stated in the 7/15/05 Office Action that the employment of different solvents in the crystallization process is an art-recognized variation for obtaining different forms.

Regarding claims 1, 2 and 4-37, Appellants noted in their Appeal Brief that these claims are directed to crystalline Form III of (S)-repaglinide. Appellants noted that Grell I discloses in Example 3 two crystalline forms of (S)-repaglinide having solid state characteristics (e.g., X-ray diffraction pattern, IR spectra, melting point) distinctly different from that of the instant crystalline Form III of (S)-repaglinide (*see* col. 85, line 40 to col. 86, line 50). Similarly, Grell II discloses two forms of (S)-repaglinide in Table III having melting points similar to the high-melt and low-melt forms of Grell I, and thus different from that of Form III. Brittain merely teaches that solid compounds may exist in different crystalline forms or polymorphs (but does not specifically mention (S)-repaglinide), and thus adds nothing over the Grell references.

Appellants indicated that the proper test for obviousness in this case is not whether the existence of (S)-repaglinide polymorphs is suggested by the prior art, but whether it would have been obvious to make the particular Form III of (S)-repaglinide form claimed in the instant application. Appellants noted that the references cited by the Examiner suggest at most the possibility of other (S)-repaglinide polymorphs. The Examiner pointed to nothing in the cited references, however, that would suggest to one skilled in the art the particular Form III claimed in the instant application, or a method for its preparation. Because of the unpredictability of polymorph prediction, Appellants submitted that no *prima facie* case for obviousness of claims 1, 2 and 4-37 under § 103(a) had been made out.

Regarding claims 50, 51, 53, 54, 56 and 57, Appellants noted in their Appeal Brief that these claims are directed to a process for preparing a crystalline Form II of (S)-repaglinide having an X-ray powder diffraction pattern substantially as shown in Table 3, the process comprising: (a) providing a solution of (S)-repaglinide in an aromatic hydrocarbon solvent, with the proviso that said solvent does not include petroleum ether; (b) cooling said solution to separate a solid mass; and (c) isolating said solid mass to provide the crystalline Form II of (S)-repaglinide.

Appellants indicated that, contrary to the Examiner's position, the proper test for obviousness is not whether the use of different solvents is expected to result in different forms, but, as with claims 1, 2 and 4-37, whether it would have been obvious to make a particular form using the claimed process based on the prior art. Although crystalline

Form II of (S)-repaglinide is acknowledged by Appellants to be a prior art form, the Examiner has pointed to nothing in the prior art that would suggest Appellants' claimed process for obtaining Form II, or a reasonable expectation of success. Appellants noted that they, and they alone, disclose that crystalline Form II of (S)-repaglinide can be prepared from a solvent containing an aromatic hydrocarbon but does not include petroleum ether (*see* page 9, ¶ 0037). Nothing in the prior art suggests that such a process would yield crystalline Form II of (S)-repaglinide. As such, Appellants submitted that no *prima facie* case for obviousness of claims 50, 51, 53, 54, 56 and 57 under § 103(a) had been made out, and the rejection should not be sustained.

In the Examiner's Answer, the Examiner stated that Appellants arguments regarding the *prima facie* obvious nature of the claimed polymorphs were not persuasive. A Wikipedia 2006 article on polymorphism was newly cited for the proposition that "every compound has different polymorphic forms, and that, in general, the number of forms known for a given compound is proportional to the time and money spent in research on that compound." Because, according to the Examiner, the compound of Grell I is identical to the instant compound (i.e., same IR spectra), and Grell I discloses variations in the process for making the instant compound, employing further variations flow naturally from the teachings of the prior art, which would proportionally increase the number of crystal forms, i.e., making the invention *prima facie* obvious.

With regard to claims 50, 51, 53, 54, 56 and 57 specifically, the Examiner stated in the Examiner's Answer that the claims are drawn to amorphous and polymorphic form III of repaglinide – repaglinide Form II was not under examination. According to the Examiner, nowhere in the claims is the issue of "aromatic hydrocarbon that does not include petroleum ether" recited.

Appellants first question the propriety of citing a Wikipedia article as valid prior art, given the non-refereed nature of the material and the fact that anyone can modify the article without respect to their level of expertise. In any event, even assuming the validity of the article, Appellants maintain that that the proper test for obviousness in this case is not whether the existence of (S)-repaglinide polymorphs is suggested by the prior art, but whether it would have been obvious to make the <u>particular</u> Form III of (S)-

repaglinide form claimed in the instant application. The Examiner has still pointed to nothing in the cited references that would suggest to one skilled in the art the particular Form III claimed in the instant application, or a method for its preparation. As discussed above with respect to Rejection (b), the Examiner is mistaken that the IR spectrum for the racemic repaglinide of Grell I is the same as the IR spectrum for the instant Form III of (S)-repaglinide.

Regarding claims 50, 51, 53, 54, 56 and 57, Appellants submit that the Examiner is mistaken that these claims are not directed to polymorphic form II of (S)-repaglinide and do not have a proviso that the "aromatic hydrocarbon does not include petroleum ether." Claim 50 reads as follows:

> A process for preparing a crystalline Form II of (S)-repaglinide, having an X-ray powder diffraction pattern substantially as shown in Table 3, said process comprising:
>
> (a) providing a solution of (S)-repaglinide in an aromatic hydrocarbon solvent, with the proviso that said solvent does not include petroleum ether;
>
> (b) cooling said solution to separate a solid mass; and
>
> (c) isolating said solid mass to provide the crystalline Form II of (S)-repaglinide.

As such, Appellants maintain that the proper test for obviousness is not whether the use of different solvents is expected to result in different polymorphic forms, but whether it would have been obvious to make a particular form using the claimed process based on the prior art. Although crystalline Form II of (S)-repaglinide is acknowledged by Appellants to be a prior art form, the Examiner still has pointed to nothing in the prior art that would suggest Appellants' claimed process for obtaining Form II, or a reasonable expectation of success. Appellants maintain that they, and they alone, disclose that crystalline Form II of (S)-repaglinide can be prepared from a solvent containing an aromatic hydrocarbon but does not include petroleum ether, and that, contrary to the Examiner's position, such evidence is relevant to claims 50, 51, 53, 54, 56 and 57. Nothing in the prior art suggests that such a process would yield crystalline Form II of (S)-repaglinide.

Accordingly, Appellants maintain that claims 1, 2, 4-37, 50, 51, 53, 54, 56 and 57 are not rendered obvious by Grell I in view of Grell II and Brittain under § 103(a), and the rejection should not be sustained.

D. Rejection of Claims 8-18 Under 35 U.S.C. § 112, First Paragraph

Claims 8-18 stand finally rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. According to the Examiner in the 7/15/05 Office Action, there is a lack of enablement as to whether the particular form can be maintained in the claimed compositions.

The Appellants indicated in their Appeal Brief that claims 8-18 contain no limitation requiring that the crystalline Form III of (S)-repaglinide be maintained indefinitely, or that it be the only form present in the composition, and Appellants submit that it is error to read such a limitation into the claims. The Appellants noted that the instant specification clearly describes and enables the preparation of compositions comprising crystalline Form III of (S)-repaglinide (*see, e.g.*, pages 15-16, ¶ 0056; pages 21-24, ¶¶ 0062-0073). Furthermore, the specification clearly describes and enables methods for identifying and monitoring the crystalline form in the claimed compositions before, during and after their preparation (*see, e.g.*, page 16, ¶¶ 0053-0054; page 18, ¶ 0057).

In the Examiner's Answer, the Examiner stated that the preponderance of evidence in the state-of-the-art indicates that pharmaceutical compositions containing any particular crystalline form cannot be assumed but must be described and enabled with specificity and particularity. Four new references are provided as supporting the Examiner's position: 1) Muzaffar et al., *J. Pharmacol.* 1:59-66 (1979) ("Muzaffar"); 2) Jain et al., *Indian Drugs* 23:315-329 (1986) ("Jain"); 3) Doelker, *Ann. Pharm. Fr.* 60:161-176 (2002) ("Deolker"); and 4) Otsuka et al., *Chem. Pharm. Bull.* 47:852-856 (1999) ("Otsuka").

The quote from p. 60 of Muzaffar in the Examiner's Answer is believed representative of the Examiner's position on this issue:

> At any one temperature and pressure only one crystal form of a drug is stable and any other polymorph existing under these conditions will convert to the stable form . . . .

Given this possible polymorphic conversion, the Examiner believes that the instant specification lacks guidance regarding the excipients and processing parameters necessary to formulate crystalline Form III of (S)-repaglinide into a composition.

As the Appellants indicated in their Appeal Brief, claims 8-18 contain no limitation requiring that the crystalline Form III of (S)-repaglinide be maintained in the composition indefinitely, or that it be the only form present in the composition, and Appellants maintain that it is error to read such a limitation into the claims. All that is necessary to meet the enablement requirement is that the information contained in the disclosure of an application must be sufficient to inform those skilled in the relevant art how to both make and use the claimed invention. *See* MPEP § 2164. Further, it is well-known that even metastable polymorphic forms can undergo conversion very slowly, as discussed at page 60 of the article by Muzaffar et al. (cited in the Examiner's Answer): the rate of conversion of a metastable form can be so slow as to be negligible.

Here, the Examiner appears to take exception with the fact that the instant specification did not provide working examples of compositions containing crystalline Form III of (S)-repaglinide. However, compliance with the enablement requirement does not turn on whether an example is disclosed, as discussed in MPEP § 2164.02:

> An applicant need not have actually reduced the invention to practice prior to filing. In *Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987), as of Gould's filing date, no person had built a light amplifier or measured a population inversion in a gas discharge. The Court held that "The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." 822 F.2d at 1078, 3 USPQ2d at 1304 (quoting *In re Chilowsky*, 229 F.2d 457, 461, 108 USPQ 321, 325 (CCPA 1956)). The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970).

As noted in the Appellants' Appeal Brief, the instant specification clearly describes and enables the preparation of compositions comprising crystalline Form III of (S)-repaglinide (*see, e.g.*, pages 15-16, ¶ 0056; pages 21-24, ¶¶ 0062-0073). Regarding the possibility of polymorph conversion during formulation, the specification

clearly describes and enables methods for identifying and monitoring the crystalline form in the claimed compositions before, during and after their preparation (*see, e.g.*, page 16, ¶¶ 0053-0054; page 18, ¶ 0057). In fact, these are the same methods described in Jain. Any composition lacking detectable Form III is simply outside the scope of claims 8-18.

Accordingly, Appellants maintain that no case for lack of enablement of claims 8-18 under § 112, first paragraph, has been made out, and the rejection therefore should not be sustained.

CONCLUSION

Appellants maintain that claims 1-2, 4-38, 40-48, 50, 51, 53, 54, 56 and 57 fully meet the requirements for patentability under §§ 102, 103 and 112. Accordingly, reversal of the Examiner's rejections is appropriate and is respectfully solicited.

Respectfully submitted,

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